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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/783,297	02/20/2004	Ning Qin	PRD-2041NP	7754

27777 7590 08/14/2006

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EXAMINER	
RAGHU, GANAPATHIRAM	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 08/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/783,297	QIN ET AL.	
	Examiner	Art Unit	
	Ganapathirama Raghu	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *65-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *65-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Application Status

In response to the Office Action letter dated Jan. 28, 2006, Applicants' filed a response and amendment, received July 03, 2006. Said amendment, cancelled claims 1-64 and filed a new set of claims 65-71. Thus, claims 65-71 are pending in the instant Office Action and are now under consideration.

Objections and rejections not reiterated from previous action are hereby withdrawn as the rejected claims have been cancelled.

Claim Objections

Claims 65-71 are all objected, because they all contain subject matter to non-elected inventions. Claims are considered to the extent of elected sequence SEQ ID NO: 3 and the corresponding polypeptide SEQ ID NO: 4.

New-Claim Rejections: 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 71 is indefinite in the recitation of " selectively hybridizes" and the conditions for hybridization, . Perusal of the specification indicates there is no definition for the conditions, which are intended to be selectively hybridizing conditions and clearly what conditions are selectively hybridizing condition varies widely depending on the individual situation as selectivity depends on what other nucleic acids are present. As such it is unclear how

homologous to the sequence of a gene encoding a polypeptide having an amino acid sequence of SEQ ID NO: 4, a sequence must be to be included within the scope of these claims.

New-Claim Rejections 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 66, 68 and 70-71 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus i.e., an isolated nucleic acid molecule comprising a nucleotide sequence of SEQ ID NO: 3 or the complementary sequence thereof, expression vector, host cell and a kit comprising said nucleic acid molecules.

As discussed in the written description guidelines the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to

reflect the variation within the genus. The specification does not contain any disclosure of the function of all polynucleotides comprising SEQ ID NO: 3 or encoding a polypeptide comprising SEQ ID NO: 4. The genus of cDNAs that comprise these above cDNA molecules is a large variable genus with the potentiality of encoding many different proteins. Therefore, many functionally unrelated DNAs are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus, i.e., SEQ ID NO: 9 having cyclooxygenase-3a (Cox-3a) activity, which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 65, 67 and 69 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not disclosed in the specification in such a way as to reasonably convey to one of skilled in the relevant art that the invention(s), at the time the application was filed, had possession of the claimed invention.

Claims 65, 67 and 69 are directed to a genus of nucleic acids encoding a polypeptide having Cox-3 activity and comprising amino acids 1-30 of SEQ ID NO: 4. The specification does not contain any disclosure of the structure of all nucleic acid sequences included in the claimed genera i.e., polypeptide having Cox-3 activity. The genus of nucleic acids claimed is

large variable genus with the potentiality of encoding many different proteins. Therefore, many structurally distinct nucleic acids are encompassed within the scope of the claims. The specification discloses only a single species of claimed genus (i. e. that of SEQ ID NO: 8) encoding SEQ ID NO: 9 as human cyclooxygenase- 3a (Cox-3a) protein comprising the amino acid sequence encoded by exon 1 of human COX-1, an insertion of 31 amino acids (SEQ ID NO: 4) encoded by intron 1 of human COX-1 after RNA editing (SEQ ID NO: 3) to the amino acid sequence encoded by exon 2 to 11 of human COX-1 (page 23). However, there is no disclosure regarding the segment of the polynucleotide of SEQ ID NO: 3 encoding the polypeptide of SEQ ID NO: 4 with the associated function of Cox-3a, which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. A sufficient written description of a genus of DNAs may be achieved by a recitation of structural features common to members of genus, **which features constitute a substantial portion of the genus**. The recited structural feature of the genus (i.e., encodes a polypeptide comprising a fragment of 30 amino acids of SEQ ID NO: 4) does not constitute a substantial portion of the genus as the remainder of the structure of any nucleic acid encoding a polypeptide having the Cox-3 enzyme activity is completely undefined and the specification does not define the remaining structural features necessary for members of the genus to be selected. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed. Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov <http://www.uspto.gov>.

Claims 65-71 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid molecule of SEQ ID NO: 8 encoding a full-length polypeptide of SEQ ID NO: 9, does not reasonably provide enablement for any polynucleotide encoding any cyclooxygenase-3 enzyme or variants or mutants and recombinants or any polynucleotide encoding a Cox-3a enzyme having the amino acid sequence of SEQ ID NO: 4 (an amino terminal fragment of Cox-3a) or any polynucleotide comprising SEQ ID NO: 3 vector and host cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with the claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 65-71 are so broad as to encompass any polynucleotide including variants or mutants and recombinants encoding a cyclooxygenase-3 enzyme, said polypeptide comprising the amino acid sequence of SEQ ID NO: 4 (an amino terminal fragment of Cox-3a) or any polynucleotide comprising SEQ ID NO: 3, vector and host cell. The scope of the claims are not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides broadly encompassed by the claims. Since the amino acid sequence

of a protein encoded by a polynucleotide determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires knowledge and guidance with regard to which amino acids in the protein's sequence and the respective codons in its polynucleotide, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the encoded proteins' structure relates to its function. However, in this case the disclosure is limited to the full length Cox-3a of SEQ ID NO: 8 comprising an amino terminal nucleotide sequence of Cox-3a enzyme of SEQ ID NO: 3 and encoding a fragment of Cox-3a having an amino acid sequence of SEQ ID NO: 4, splice variant retaining almost the entire intron 1 but is missing a guanidine at position 64 leading to a short and self-rectifying shift in the reading frame, vector and isolated host cell. It would require undue experimentation of the skilled artisan to make and use the claimed encoding polynucleotides. The specification is limited to teaching the use of a an amino terminal nucleotide sequence of Cox-3a enzyme of SEQ ID NO: 3 and encoding a fragment of Cox-3a having an amino acid sequence of SEQ ID NO: 4, splice variant retaining almost the entire intron 1 but is missing a guanidine at position 64 leading to a short and self-rectifying shift in the reading frame and the full-length Cox-3a gene of SEQ ID NO: 8, but provides no guidance with regard to the making of other variants and mutants from any source or with regard to other uses. In view of the great breadth of the claims, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495), the

claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by these claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is not routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions or deletions.

The specification does not support the broad scope of the claims which encompass all modifications of any polynucleotide encoding a cyclooxygenase-3 enzyme or variants or mutants and recombinants, comprising the amino acid sequence of SEQ ID NO: 4 (an amino terminal fragment of Cox-3a) or any polynucleotide comprising SEQ ID NO: 3, vector and host cell, because the specification does not establish: (A) any cyclooxygenase-3 enzyme or variants or mutants and recombinants, said polypeptide having the amino acid sequence of SEQ ID NO: 4 (an amino terminal fragment of Cox-3a) and encoded by the polynucleotide of SEQ ID NO: 3 and having Cox-3a activity; (B) a rational and predictable scheme for identification of amino terminal fragments of Cox-3a with an expectation of obtaining the desired biological function, i.e., Cox-3a activity; and (C) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including polypeptides with an enormous number of modifications. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of polypeptides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 69-70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, because, while claims 69-70 are enabling for an isolated host cell transformed with the synthetic nucleic acid i.e., an isolated nucleic acid molecule encoding a fragment of cyclooxygenase-3 enzyme wherein the fragment comprises the amino acid sequence of SEQ ID NO: 4, expression vector and isolated host cell (claim 69) or enabling for an isolated host cell transformed with the synthetic nucleic acid i.e., an isolated nucleic acid molecule comprising a nucleotide sequence of sequence of SEQ ID NO: 3, expression vector and isolated host cell (claim 70), does not reasonably provide enablement for transgenic multi-cellular organisms or host cells within a multi-cellular organism that have been transformed with said synthetic nucleic acids. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 69-70 are so broad as to encompass host cells transformed with specific nucleic acids, including cells in *in vitro* culture as well as within any multi-cellular organism. The scope of the claims are not commensurate with the enablement provided by the disclosure with regard to extremely large number of transformed host cells broadly encompassed by the claims. While methods for transforming cells *in vitro* are well known in the art, methods for successfully transforming cells within complex multi-cellular organisms are not routine and are highly unpredictable. Furthermore, methods for producing a successfully transformed cell within the multi-cellular organism are unlikely to be applicable to transformation of other types of multi-cellular organism as multi-cellular organisms vary widely. However, in this case the disclosure is limited to only isolated host cells *in vitro*. Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including the use of host cells within a multi-cellular organism for the production of polypeptide. The scope of claim must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA)). Without sufficient guidance, expression of genes in a particular host cell and having the desired biological characteristics is unpredictable, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F. 2d 731, 8 USPQ 2nd 1400 (Fed. Cir., 1988). It is suggested that the applicants limit the claims to "An isolated host cell ...".

Maintained-Claim Rejection: 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 66, 68 and 70 are rejected under 35 U.S.C. 102(b) as being anticipated by Wang et al., (Biochem. Biophys. Res. Commun., 190(2): 406-411, 1993). Claims 66, 68, 70-71 are drawn to a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 3 or the complementary sequence thereof , to an expression vector host cell and a kit comprising the said nucleic acid molecule. Wang et al., (*supra*), disclose an isolated polynucleotide (Accession NO: L08404) sequence, which has 100% homology to the SEQ ID NO: 3 of the instant application, designated as the promoter of human prostaglandin H synthase-1 gene. The reference also discloses vectors and host cells comprising said polynucleotides (Materials and Methods section, paragraph 6, page 407). Therefore, Wang et al., (*supra*) anticipate claims 66, 68 and 70 as written (see copy of the sequence alignments provided).

Claim Rejections 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 71 rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al., (Biochem. Biophys. Res. Commun., 190(2): 406-411, 1993). Claim 71 is directed to a kit comprising a nucleic acid probe that selectively hybridizes to a nucleic acid molecule encoding a polypeptide having an amino acid sequence of SEQ ID NO:4. Wang et al., (*supra*), disclose an isolated polynucleotide (Accession NO: L08404) sequence, which has 100% homology to the SEQ ID NO: 3 of the instant application, designated as the promoter of human prostaglandin H synthase-1 gene. The reference also discloses vectors and host cells comprising said polynucleotides (Materials and Methods section, paragraph 6, page 407). However said reference is silent regarding a kit comprising a nucleic acid probe that selectively hybridizes to a nucleic acid molecule encoding a polypeptide having an amino acid sequence of SEQ ID NO: 4, since SEQ ID NO: 4 is encoded by the polynucleotide of SEQ ID NO: 3. It would have been obvious to one of ordinary skill in the art to use the said sequence as a probe for isolation or identification of sequences comprising said sequence and as said sequence is available in a vector form and therefore could be easily reconstituted in suitable buffer system to make a kit comprising the said

nucleic acid molecule. One of ordinary skill in the art would have been motivated to make such a kit and would have had a reasonable expectation of success, as Wang et al., disclose an isolated polynucleotide designated as the promoter of human prostaglandin H synthase-1 gene and cyclooxygenases are involved in the synthesis of prostaglandins that are involved in inflammatory processes. Therefore all the proteins involved in the inflammatory pathways are drug targets and a kit would be useful to detect any changes in gene expression or modulation of the activity of cyclooxygenases.

Summary of Pending Issues

The following is a summary of issues pending in the instant application.

1) Claims 65-71 are objected, because they all contain subject matter to non-elected inventions.

2) Claim 71 is rejected under 35 USC § 112, second paragraph for as being indefinite for failing to particularly point out and distinctly claim the subject matter.

3) Claims 65-71 are rejected under 35 USC § 112, first paragraph for written description enablement.

4) Claims 66, 68 and 70 are rejected under 35 USC § 102 (b) as being anticipated by Wang et al., (Biochem. Biophys. Res. Commun., 190(2): 406-411, 1993).

5) Claim 71 rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al., (Biochem. Biophys. Res. Commun., 190(2): 406-411, 1993).

Conclusion

None of the claims are allowable. Claims 65-71 are rejected for the reasons identified in the Rejections and Summary sections of this Office Action. Applicants must respond to the objections/rejections in each of the sections in this Office Action to be fully responsive for prosecution.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathirama Raghu whose telephone number is 571-272-4533. The examiner can normally be reached on 8 am - 5 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of the application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ganapathirama Raghu, Ph.D.
Patent Examiner
Art Unit 1652

July 30, 2006.

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GROUP ~~1800~~ 1600